EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Glybera

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
PSUSA/10056 /201610	Periodic Safety Update EU Single assessment - alipogene tiparvovec	05/05/2017	n/a		PRAC Recommendation - maintenance
S/0057	4th Annual Re-assessment	23/02/2017	20/04/2017	SmPC, Annex II, Labelling and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation of Glybera should be maintained.

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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IB/0061	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	28/02/2017	n/a		
PSUSA/10056 /201604	Periodic Safety Update EU Single assessment - alipogene tiparvovec	01/12/2016	n/a		PRAC Recommendation - maintenance
IB/0059	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	17/11/2016	n/a		
IA/0058	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	08/11/2016	n/a		
II/0056	To change the acceptance criteria for the finished product specification. B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	13/10/2016	n/a		
PSUSA/10056 /201510	Periodic Safety Update EU Single assessment - alipogene tiparvovec	13/05/2016	n/a		PRAC Recommendation - maintenance
IA/0054	B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits	10/03/2016	n/a		

S/0051	3rd Annual Re-assessment	28/01/2016	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation of Glybera should be maintained.
II/0048	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	28/01/2016	n/a		
II/0047	B.II.a.3.b.3 - Changes in the composition (excipients) of the finished product - Other excipients - Change that relates to a biological/immunological product	28/01/2016	12/05/2016	SmPC, Labelling and PL	The SmPC, labelling and PIL are updated to delete calcium chloride and magnesium chloride from the list of excipients.
II/0046/G	This was an application for a group of variations. B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.a.2.b - Changes in the manufacturing process of	28/01/2016	12/05/2016	Annex II	

	the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation				
IB/0052	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	26/01/2016	n/a		
PSUSA/10056 /201504	Periodic Safety Update EU Single assessment - alipogene tiparvovec	06/11/2015	n/a		PRAC Recommendation - maintenance
IB/0049	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	25/09/2015	n/a		
II/0038	Update of sections 4.4 and 5.1 of the SmPC based on the final CSR for Study CT-AMT-011-05, a retrospective clinical records review study	24/09/2015	12/05/2016	SmPC	Study CT-AMT-011-03 was a combined retrospective and prospective study of subjects who had taken part in studies CT-AMT-010-01, CT-AMT-011-01 and CT-AMT-011-02.

	undertaken to generate further long-term follow-up data on the incidence and severity of acute pancreatitis episodes in LPLD subjects who previously participated in clinical studies with alipogene tiparvovec or AMT-10. A revised RMP version 6.0 was agreed during the procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Study CT-AMT-011-05: Further follow-up of patients who took part in study CT-AMT-011-03 (to a median of 5.8 years after exposure to Glybera) has shown a reduction in hospital stay of 1 day per patient per year when compared to the same length of time prior to exposure. SmPC section 4.4 has been updated to reflect the fact that treatment with Glybera does not eliminate attacks of acute pancreatitis. Patients are advised to continue to follow a low-fat diet and refrain from alcohol consumption.
II/0037/G	This was an application for a group of variations. Update of sections 4.8 and 5.1 of the SmPC in order to reflect new safety and efficacy data with a 5-year follow-up generated with studies CT-AMT-010-01 and CT-AMT-011-01. The Package Leaflet is updated accordingly. Further, the MAH took the opportunity to implement minor editorial changes in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	12/05/2016	SmPC and PL	Following the assessment of the data provided, some ADRs previously listed in SmPC section 4.8 are considered unlikely to be related to the product and have therefore been removed: lipaemia retinalis, xanthoma and hypoglycaemia. However, the new ADR muscle pain has been added. In SmPC section 5.1 updated information related to the study follow-up duration has been introduced and the sentence "glybera was well tolerated" has been removed to reflect the data provided.
II/0034	Update of section 5.1 of the SmPC based on the final CSR for Study CT-AMT-011-02 and its extension, including patient follow-up to 52 weeks. Further,	24/09/2015	12/05/2016	SmPC and PL	In the submitted clinical reports, serum triglyceride concentration has returned to values similar to those at baseline beyond 14 weeks after administration of Glybera.

	SmPC sections 4.4 and 4.8 of the SmPC have been updated with information related to myositis and elevations in serum creatine kinase activity. The Package Leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Clarification is therefore introduced in the SmPC section 5.1 in relation to triglyceride levels. Additionally correction is introduced in section 5.1 of the SmPC in relation to the biopsies data collection. Recipients of Glybera may display a rise in serum creatine kinase activity that becomes evident about 2 weeks after administration, peaks at around 8 weeks and then returns to baseline by week 26. One patient developed myoglobinuria in association with raised serum creatine kinase activity. Muscle biopsies obtained up to 52 weeks after administration of Glybera show an infiltrate of lymphocytes and macrophages. The long term consequences of this cellular infiltration are not known. The new ADRs 'acute myositis and chronic myositis' and 'elevations in serum creatine kinase activity' have been added to SmPC section 4.8 accordingly.
IB/0050	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	25/08/2015	n/a		
IB/0043	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/05/2015	12/05/2016	SmPC and PL	
PSUSA/10056 /201410	Periodic Safety Update EU Single assessment - alipogene tiparvovec	07/05/2015	n/a		PRAC Recommendation - maintenance
S/0039	Second Annual Re-assessment.	26/02/2015	09/04/2015	Annex II	The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the

					medicinal product, concluded that Marketing Authorisation of Glybera should be varied. Minor changes are introduced to update the status of the quality annex II obligation to update the deadline for providing the information on virus safety up to July 2015.
IA/0044	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	19/02/2015	n/a		
IA/0042/G	This was an application for a group of variations. B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.f.1.e - Stability of FP - Change to an approved stability protocol	02/02/2015	n/a		
IA/0041	B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol	23/01/2015	n/a		
PSUV/0036	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance
II/0030	Update of the protocols for the post-prandial chylomicron efficacy and safety phase IV study requested in the annex II (specific obligation 02): Protocol Number: Gly-CD-001 - An open label, multi-centre trial of Glybera (alipogene tiparvovec) for the treatment of LPLD Patients; Protocol Number: Gly-CD-002 - Evaluation of Postprandial Metabolism of Chylomicrons in Healthy	25/09/2014	11/03/2015	Annex II	N/A

	Subjects Consequently, the RMP (version 5.0) has been updated and the timelines in Annex II amended regarding the Specific obligation 02. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
IAIN/0035	Extention of submission date for a Type II variation to introduce the nanofilter as an additional manufacturing process step from 31.12.2013 to 31.10.2014. C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	17/07/2014	11/03/2015	Annex II	
II/0005	Change to drug product test method and approval of finished product quality control testing site. B.II.d.2.c - Change in test procedure for the finished product - Replacement of a biological/ immunological/immunochemical test method or a method using a biological reagent	26/06/2014	11/03/2015	Annex II	
PSUV/0031	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance

S/0027	Annual re-assessment.	20/02/2014	28/04/2014	Annex II and PL	
II/0025	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/03/2014	11/03/2015	SmPC	
IB/0032	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	03/03/2014	n/a		
II/0029	Change in finished product specification. B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	23/01/2014	n/a		
IB/0026	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	19/12/2013	28/04/2014	SmPC, Annex II and PL	
II/0024	Change to active substance testing. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS	18/12/2013	n/a		

II/0019	Change in active substance specification B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS	18/12/2013	n/a		
IB/0021	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	05/12/2013	n/a		
II/0011	Change to active substance test method B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS	21/11/2013	n/a		
IB/0015	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	15/11/2013	n/a		
IB/0028	B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test	07/11/2013	n/a		
IB/0022	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	07/11/2013	n/a		
IB/0020	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	07/11/2013	n/a		

IB/0018	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	07/11/2013	n/a		
IA/0023/G	This was an application for a group of variations. B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	18/10/2013	n/a		
IA/0017/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	17/10/2013	n/a		
IA/0016	A.7 - Administrative change - Deletion of manufacturing sites	02/10/2013	n/a		
IAIN/0014	C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to	23/09/2013	17/12/2013	SmPC and PL	

	additional monitoring				
II/0010	Change to finished product test method. B.II.d.2.c - Change in test procedure for the finished product - Replacement of a biological/ immunological/immunochemical test method or a method using a biological reagent	19/09/2013	n/a		
IB/0013	B.I.c.1.z - Change in immediate packaging of the AS - Other variation	18/09/2013	n/a		
IAIN/0012	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	10/09/2013	n/a		
IB/0009	B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	06/08/2013	n/a		
II/0006	Change to drug product test method B.II.d.2.c - Change in test procedure for the finished product - Replacement of a biological/ immunological/immunochemical test method or a method using a biological reagent	25/07/2013	17/12/2013	Annex II	
II/0008	Change to drug product test method B.II.d.2.c - Change in test procedure for the finished product - Replacement of a biological/ immunological/immunochemical test method or a	27/06/2013	17/12/2013	Annex II	

	method using a biological reagent				
II/0007	Change to drug product test method B.II.d.2.c - Change in test procedure for the finished product - Replacement of a biological/ immunological/immunochemical test method or a method using a biological reagent	27/06/2013	17/12/2013	Annex II	
II/0004	Change to drug substance test method B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS	27/06/2013	17/12/2013	Annex II	
II/0003	Change to drug substance test method B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS	27/06/2013	17/12/2013	Annex II	
IA/0002	A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	03/01/2013	17/12/2013	Annex II, Labelling and PL	
IAIN/0001	A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	21/12/2012	17/12/2013	Annex II, Labelling and	

				PL	